Nanotechnology Characterization Laboratory:

Supporting Medical Product Development for Cancer Applications

National Toxicology Program Board of Scientific Advisors

March 15, 2006

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National Cancer Institute

Objectives for Today's Presentation

NCI Alliance for Nanotechnology in Cancer

- Overview of Nanotechnology Development for Cancer Research Applications
- Rationale for a Nanotechnology Characterization Laboratory
- The Interface of Toxicology for Medical Product Development and Environmental Health and Safety Issues
- Challenges and Opportunities

The Complexity of Cancer:
The Six Aberrations of Cancer

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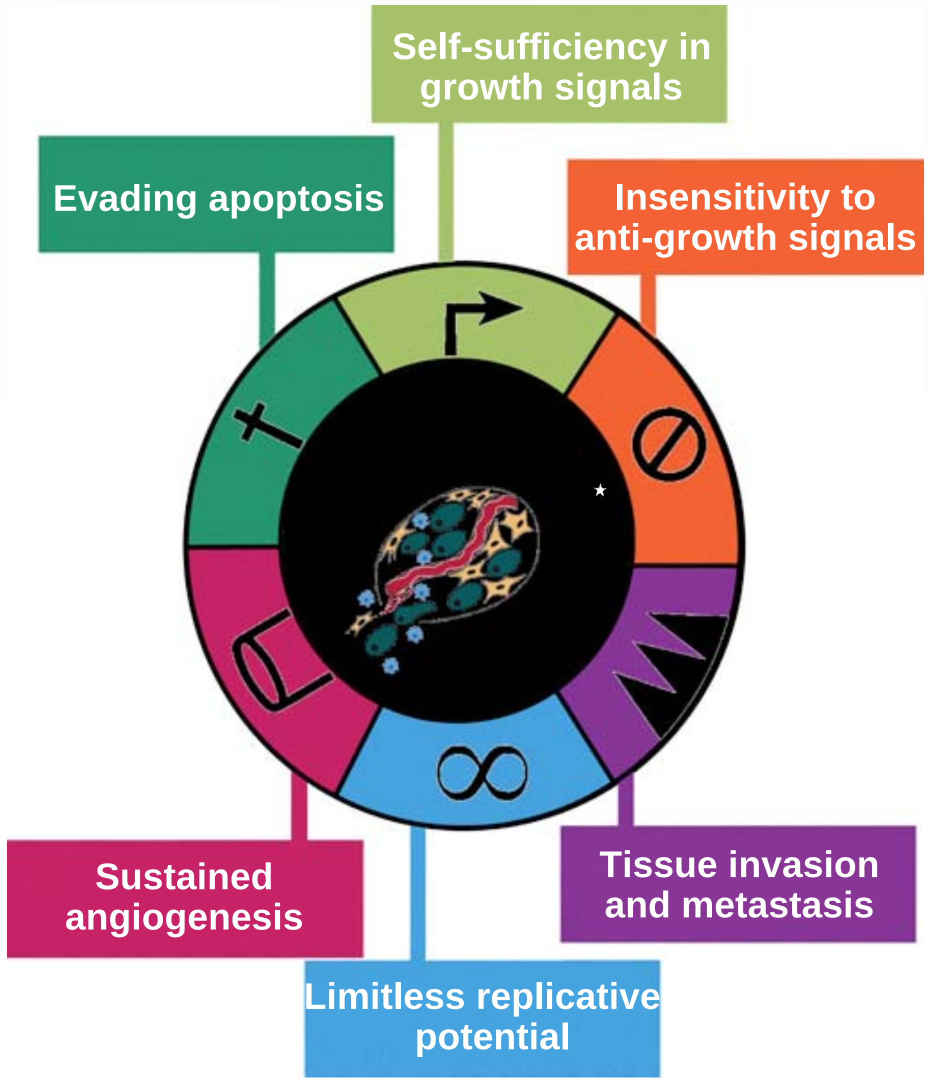
Nanotechnology
in Cancer



Hanahan & Weinberg,
Cell 100:57 (2000).

Cancer Starts with a Single Genetic Change and Proceeds Through Stages to Metastasis and Death

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Where We Must Go ← Nanotechnology Paradigm — **Where We Are**

Early Detection Prevention

Detection and Diagnosis

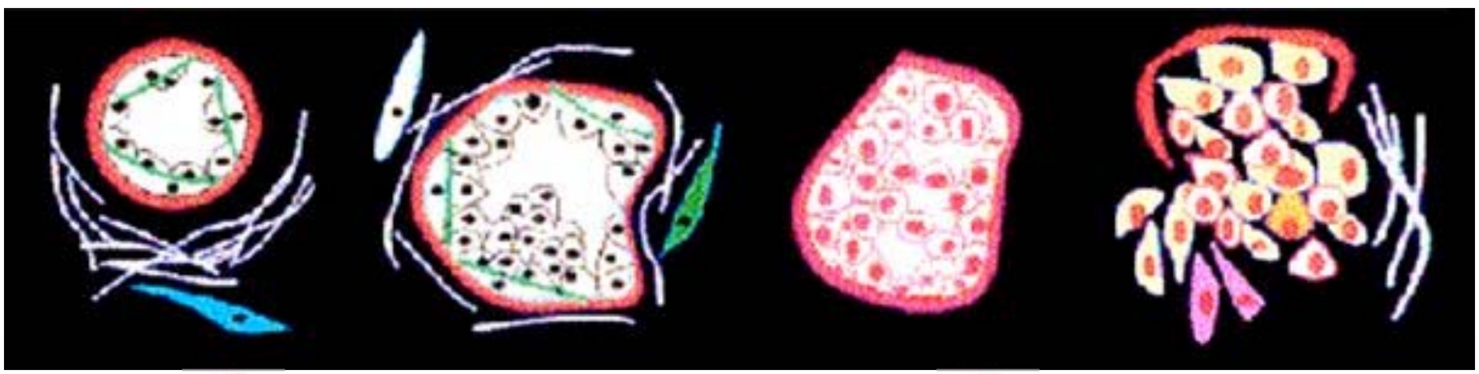
Malignant Tumors With Metastases

Year 0

Year X

Year Y

Year Z



Prevention

Prevention/Modulation/ Targeted Treatment

The Potential of Nanotechnology in Cancer

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Nanotechnology is a disruptive technology with major potential to drive a new generation of cancer diagnostics and therapeutic products.

But, realization of this potential requires systems-level changes and new product development approaches…

Why It's the Right Time: Technology and Product Development

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- The science is exploding
  - Major advances in genomics, proteomics, and materials science
  - Tidal wave of data on molecular underpinnings of disease and increased understanding of cancer mechanisms
- The nano-based biomedical product candidate is expanding*
  - 61 nanotech-based drugs and delivery systems
  - 91 devices or diagnostic tests
- The private sector is getting into the game**
  - $1.7 billion invested in nanotech in 2004
  - Steady stream of IP (88,546 U.S. patents from 1976 to 2002)
  - 109 nanotech startups have secured VC funding since 1998

* Source: 2005 Nanomedicine, Device & Diagnostic Report, National Health Information, LLC.

** Source: The Nanotech Report 2004, Lux Research.

Why It's the Right Time: Federal Funding

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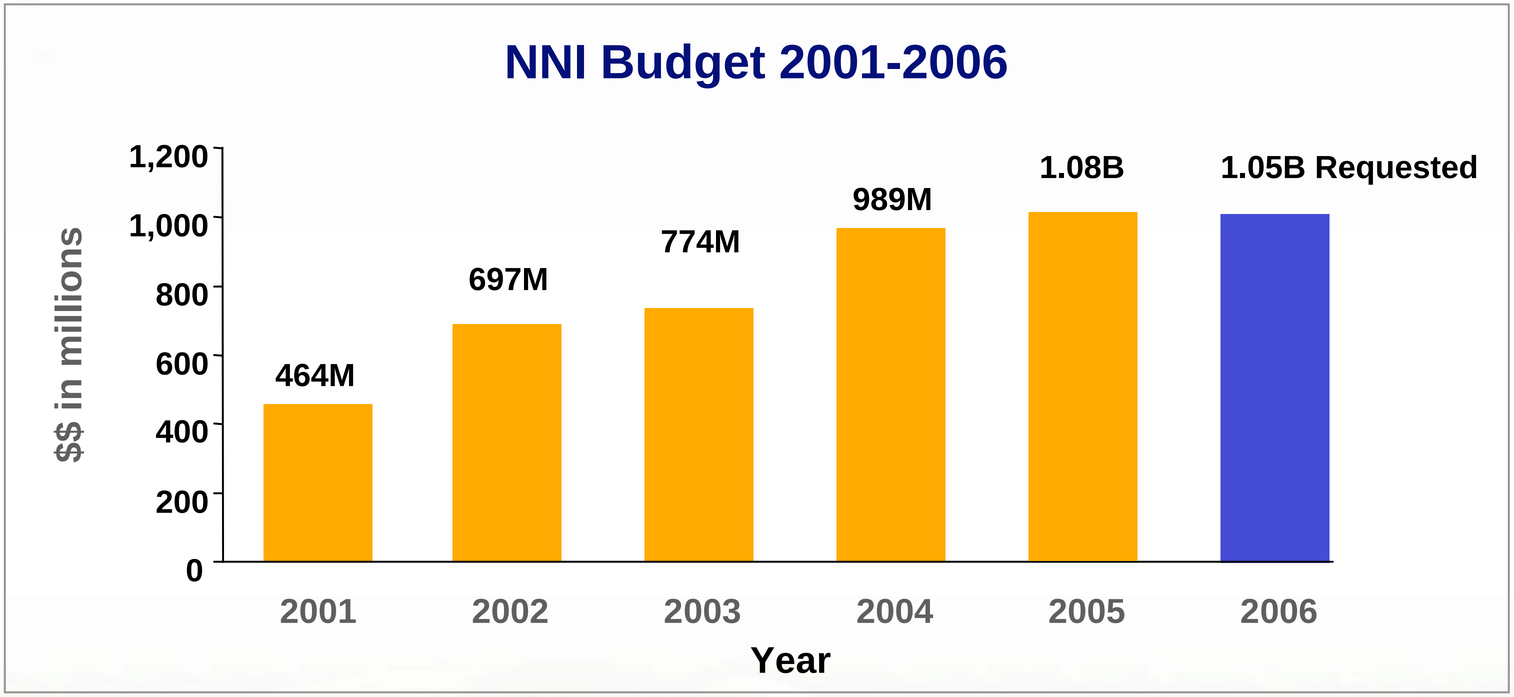
Government investment is huge

- National Nanotechnology Initiative: 2006 request for $1.05 billion



Source: National Nanotechnology Initiative (NNI).

Why It's the Right Time:
State and Regional Commitment

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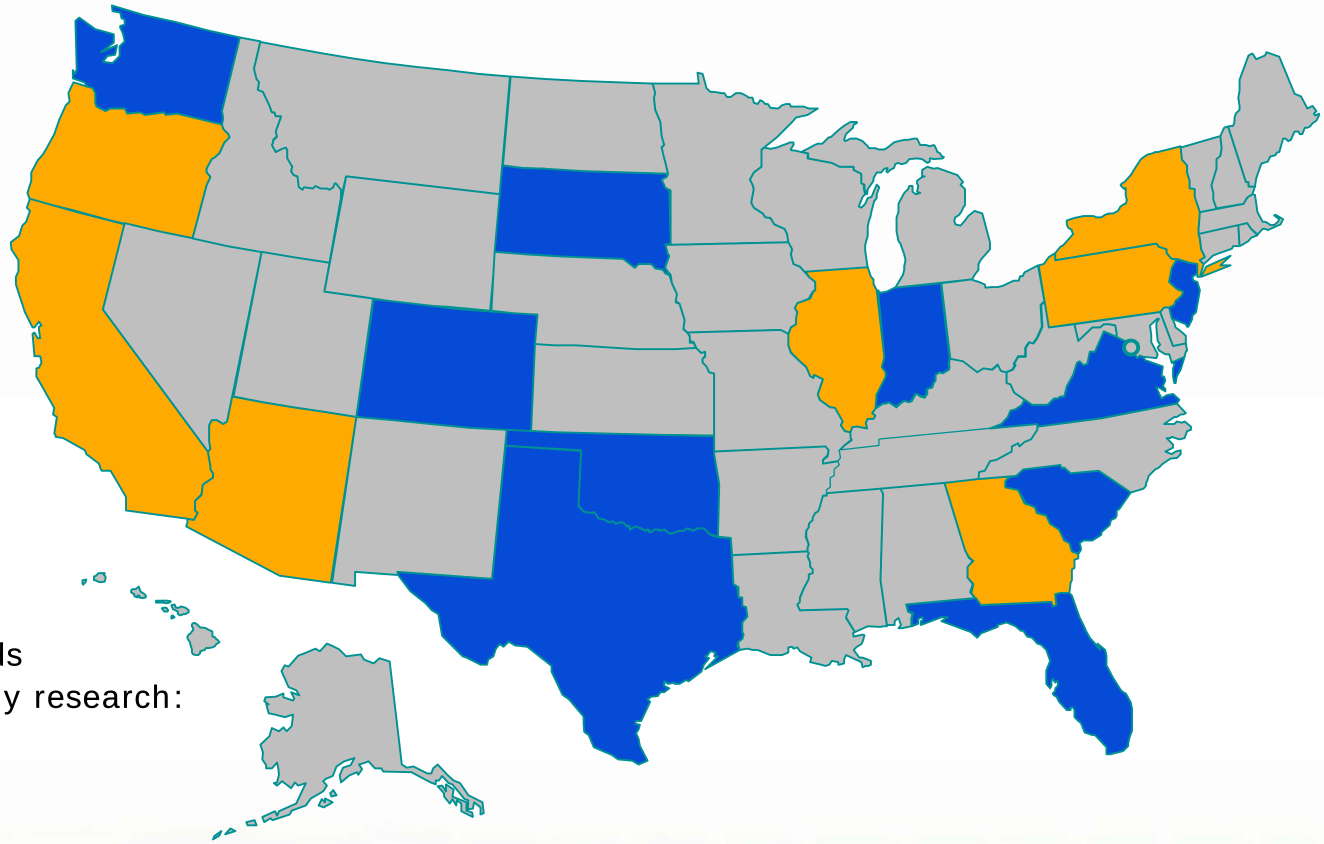
Up to $20 million
state, regional and matching funds committed:
CO, FL, IN, NJ, OK, SC, SD, TX, VA, WA

Over $20 million
state, regional and matching funds committed:
AZ, CA, GA, IL, NY, OR, PA



Total state and regional funds committed to nanotechnology research:

$864 million

Source: "*Regional, State and Local Initiatives in Nanotechnology,*" Report of the NNI Workshop, 2003.

Nanoparticle Toolbox

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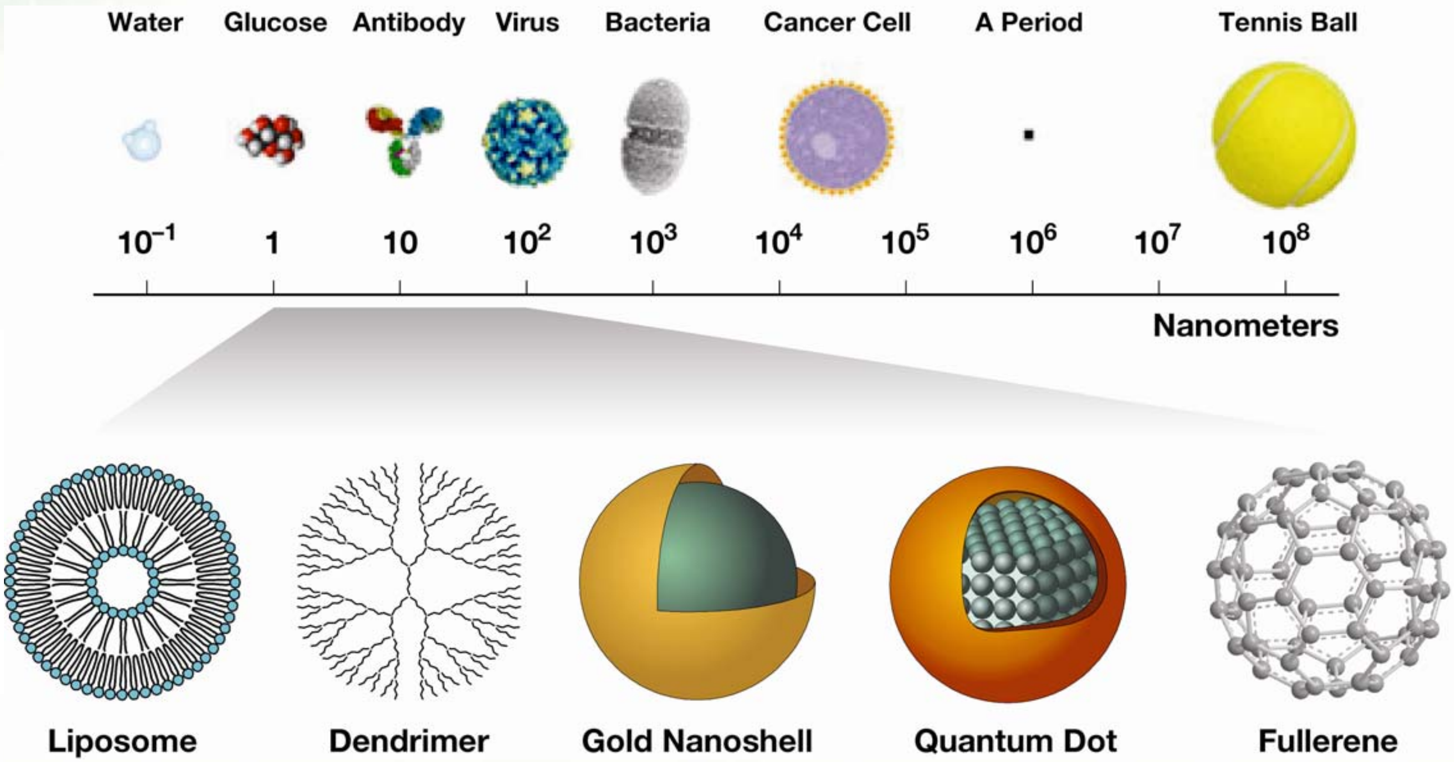

Nanoparticles for Biomedical Applications

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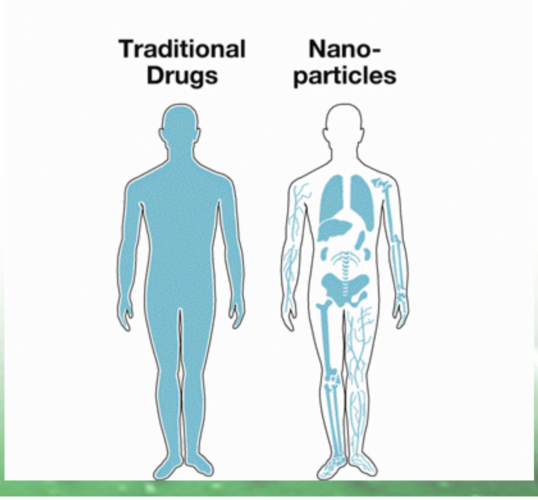
- Multiple functions:
  - Tissue targeting
    - tumor specific binding
  - Sensing or imaging capability
    - improved sensitivity
    - multi-modal imaging
  - Non-invasive treatment
    - Therapeutic localized delivery
    - Localized cell kill
    - Lower dose administered
    - Improved side effect profile

- Nanoparticles;
  - Quantum dots
  - Polymer particles
  - Dendrimers
  - Magnetic particles
  - Nanoshells
  - Nanotubes
  - Virus engineered particles



Nanotech “Toolbox” for Cancer Products

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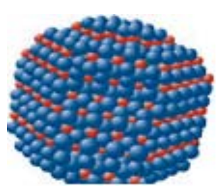
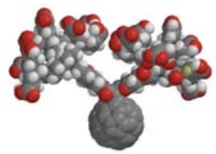
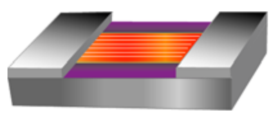
Modality		*Potential Applications*
Cantilevers		• High-throughput screening • Disease protein biomarker detection • DNA mutation detection (SNPs) • Gene expression detection
Carbon Nanotubes		• DNA mutation detection • Disease protein biomarker detection
Dendrimers		• Target sequestration • Controlled release drug delivery • Image contrast agents
Nanocrystals		• Improved formulation for poorly soluble drugs

Nanotech "Toolbox" for Cancer Products

NCI Alliance for Nanotechnology in Cancer

Modality		*Potential Applications*
Nanoparticles		• Multifunctional therapeutics • Targeted drug delivery, permeation enhancers • MRI and ultrasound image contrast agents • Reporters of apoptosis, angiogenesis, etc.
Nanoshells		• Deep tissue tumor cell thermal ablation • Tumor-specific imaging
Nanowires		• High-throughput screening • Disease protein biomarker detection • DNA mutation detection (SNPs) • Gene expression detection
Quantum Dots		• Optical detection of genes and proteins in animal models and cell assays • Tumor and lymph node visualization

Nanotech Has Multiple Applications: Detection, Treatment and Prevention

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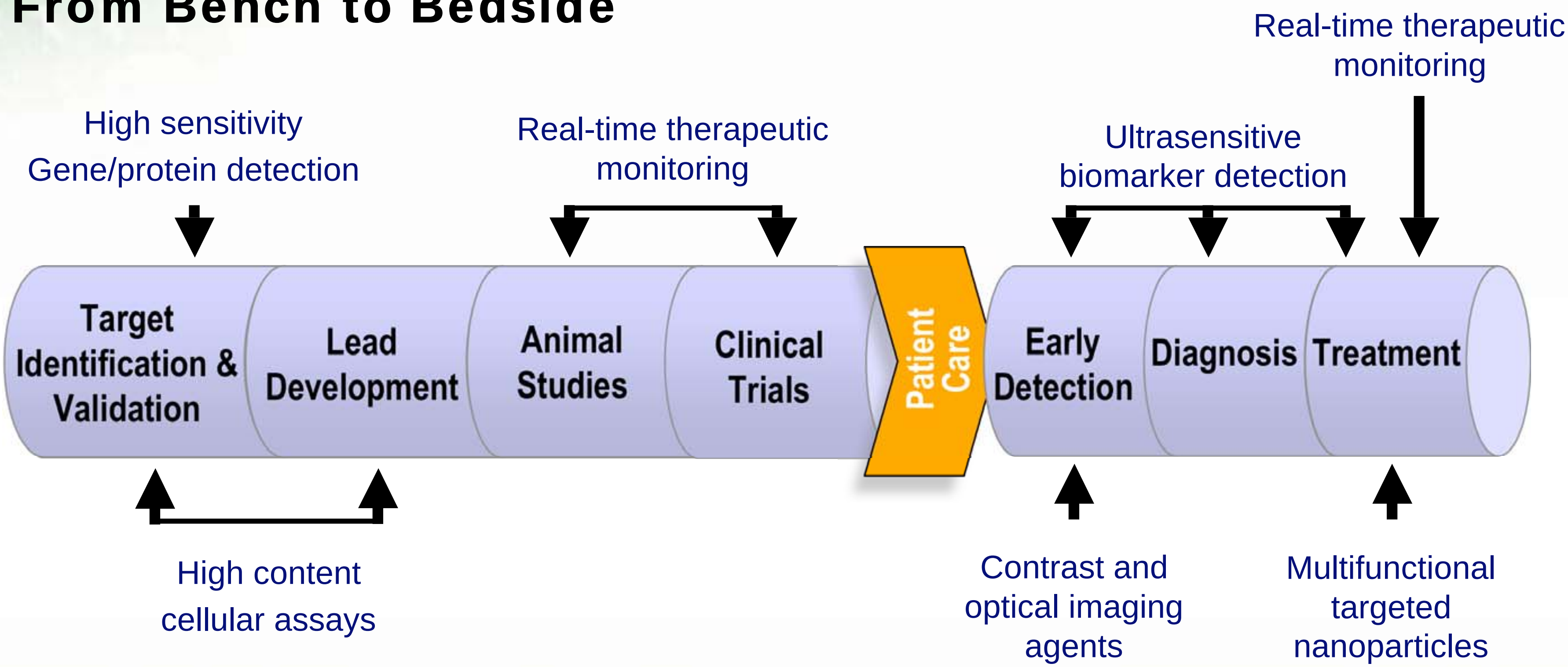
From Bench to Bedside



Nanotech Will Enable Early Detection of Cancer

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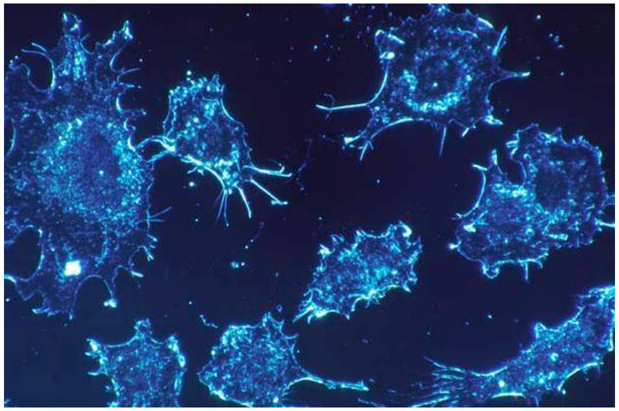
Problem:

- Cancer metastasizes before it can be detected
- Tumors are difficult to control



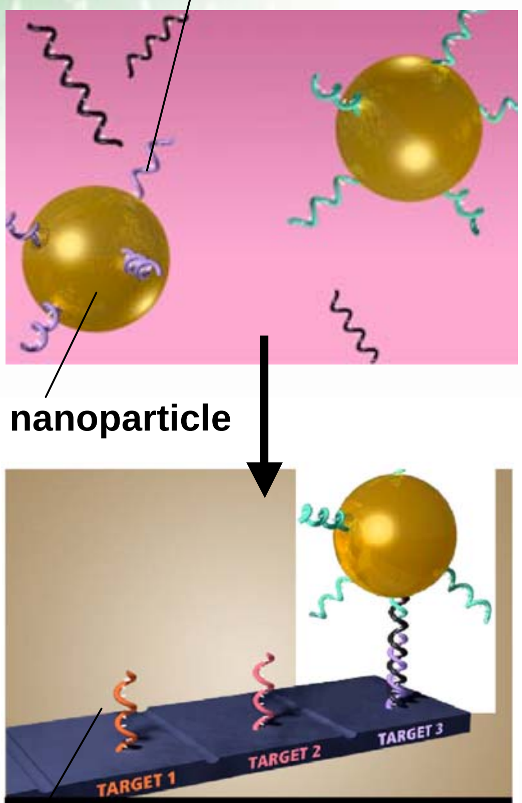
Source: NCI

Solution:

- Nanotechnology-based sensors for genetic and protein-based monitoring
  - High sensitivity and specificity
  - Label-free detection
  - DNA and protein detection on the same platform
  - *In vivo* localized sensing

Nanoparticle-based Sensors

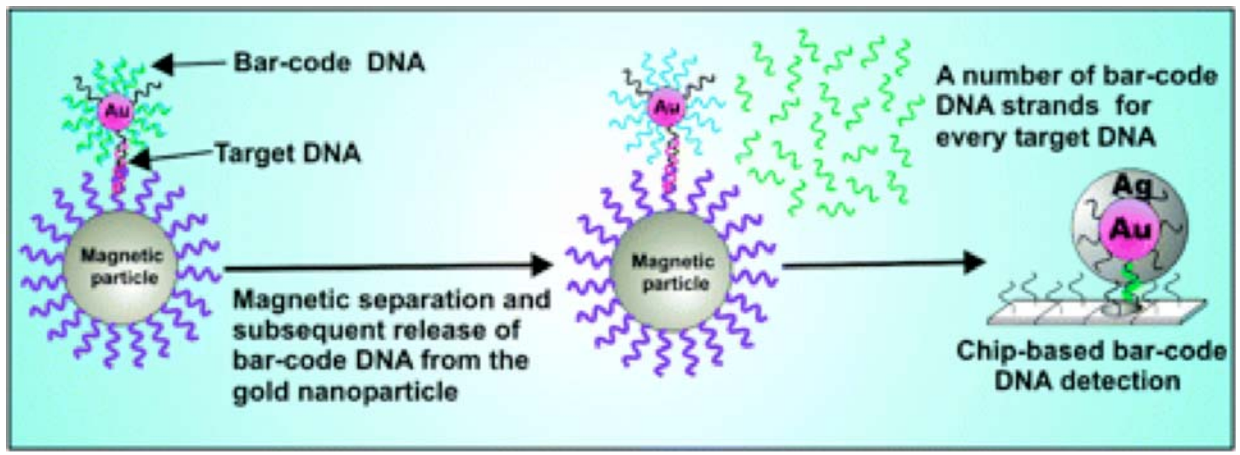
Target



Au nanoparticle

Probe

from Nanosphere (Mirkin et al.)



Nam, Mirkin et al. JACS *126*, 5932 (2004)

Nanotech Will Enable *In Vivo* and Local Imaging

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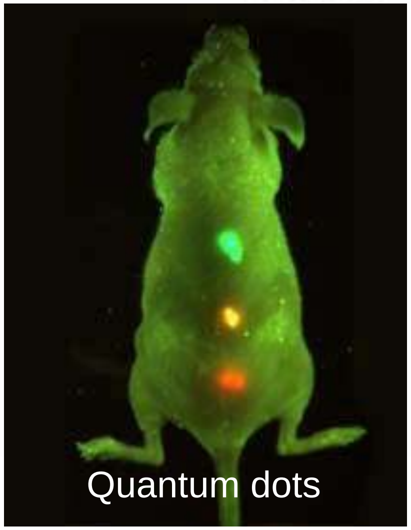
Problem:

- Cancer metastasizes before it can be detected
- Carcinogens are often hard to detect

Solution:

- Multifunctional nanoparticles functionalized with specific antibodies decorate tumor cells
- Subsequent imaging allows for pinpointing of tumor cell networks



Source: Sh. Nie, JAMA, Vol. 292, No.16, p.1944-1945, 2004.

Quantum Dots

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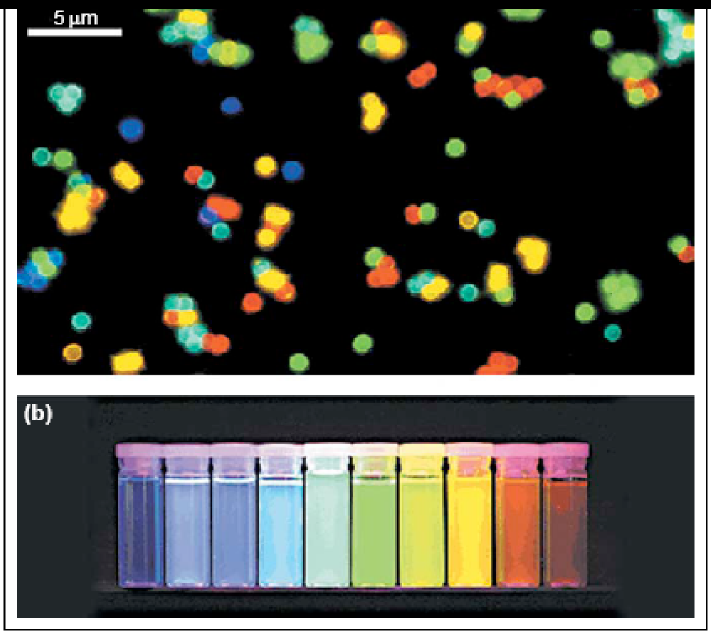
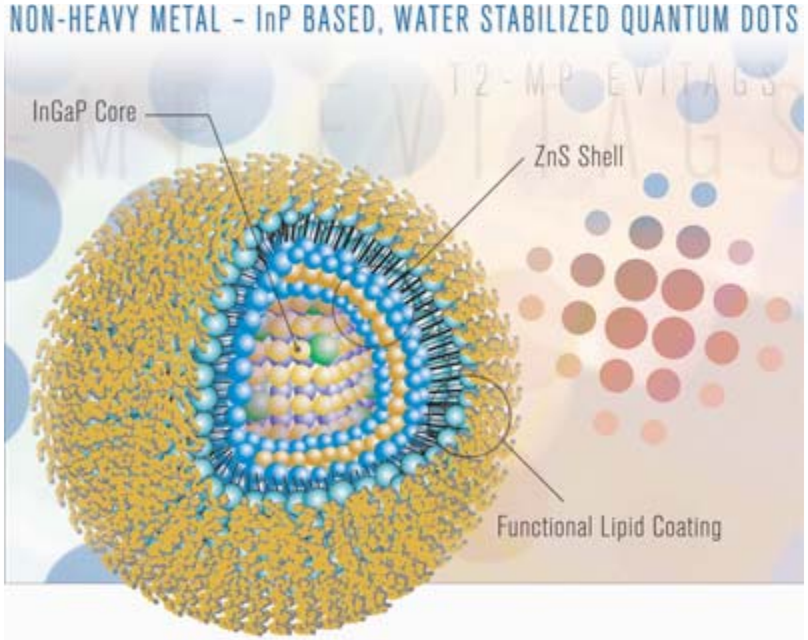
Nie et al., Nat. Biotechnol. 19, 631 (2001)



- Size dependent emission wavelength
- Good optical stability
- Excitation at single wavelength
- CdSe and CdS materials family
- Toxicity?

Evident Technologies



- NIR emission
- InP materials family
- Solve toxicity issue using coatings or novel material

Polymer particles - Drug delivery

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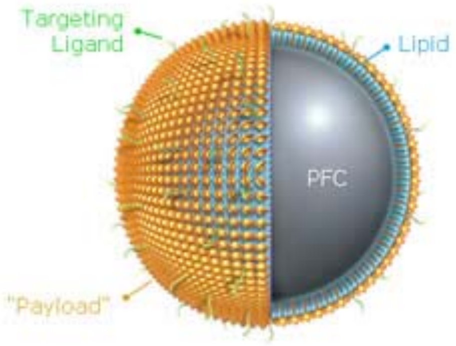
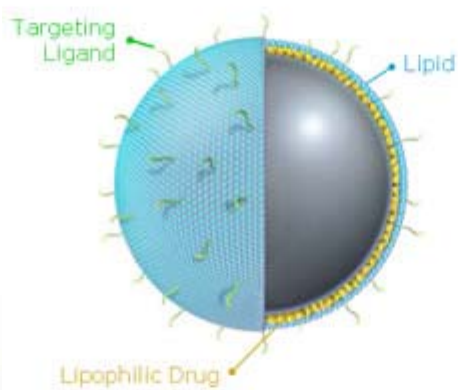
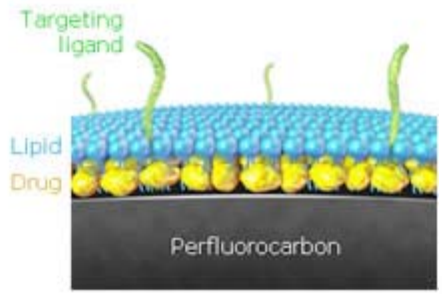






Specific
The high molecular specificity of monoclonal antibodies, small-molecule ligands and other targeting ligands for disease biomarkers translates directly into high specificity of the emulsion particles for disease sites.

Powerful
While only 10 to 100 targeting ligand molecules are need to direct and securely bind an individual emulsion particle to the disease site, each particle can carry 100,000 or more payload molecules. This "signal amplification" opens up opportunities not otherwise possible.

Biological Compatibility
Both in terms of size and composition, the emulsion particles are designed to be both safe and effective, and to avoid potential problems with distribution, metabolism or excretion.

Kereos,
G. Lanza, S. Wickline, Washington University

Case Study: NCI-sponsored Technology Integration of Multifunctional Nanoparticles

NCI Alliance for Nanotechnology in Cancer

1994 — 1st targeted ultrasound contrast agent reported

1st targeted MRI contrast agent reported

1997 — 1st patent issued to Barnes-Jewish Hospital

1999 — *Kereos incorporated: license for entire nanoparticle platform from Hospital*

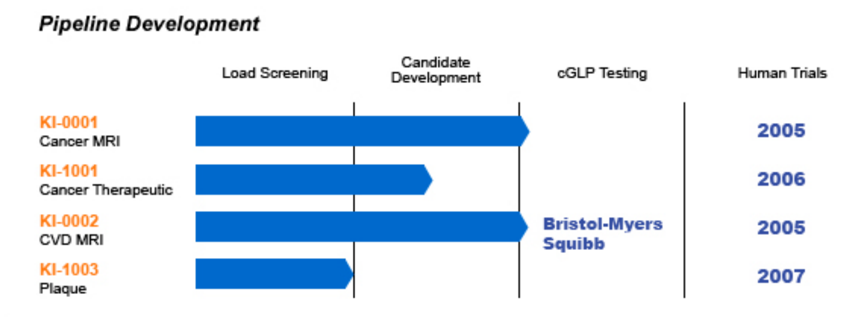
2000 — 1st NCI UIP grant (Unconventional Innovation Program)

2003 — 2nd NCI UIP grant:Kereos subcontract

2004 — (NCI DCIDE program)

Corporate Partners

- Dow Chemical
- Philips Medical Systems
- Bristol-Myers Squibb Medical Imaging



http://www.kereos.com

KEREOS TARGETED THERAPEUTICS AND MOLECULAR IMAGING

Courtesy: Kereos

Nanoscale drug delivery
Abraxane™ – paclitaxel

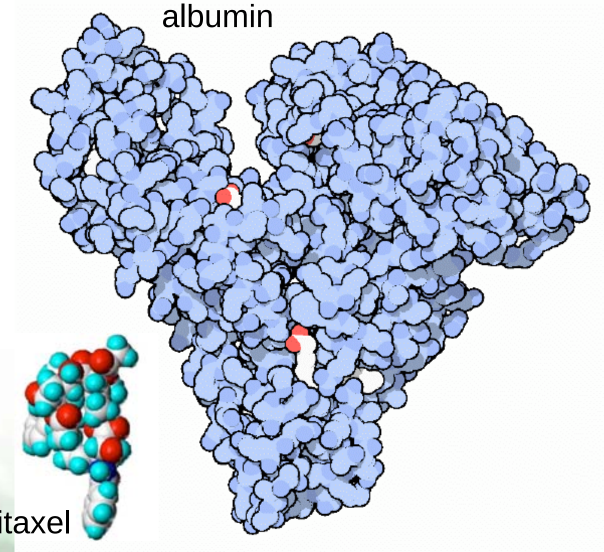
NCI Alliance for Nanotechnology in Cancer

Overcoming biological barriers

- Injectable nanoparticle albumin-bound (nab) paclitaxel, a well-known chemotherapy agent
- Protein delivery system leverages albumin (common nutrient carrier) to deliver paclitaxel intravenously without toxic solvent normally required with paclitaxel alone
- Tumor cells readily accept albumin, anticipating the nutrients it normally ferries through the blood, and instead take up paclitaxel, which is toxic to the tumor cell

Clinical trials

- Randomized comparative study of 460 advanced breast cancer patients treated with Abraxane or paclitaxel
- Results: 29% reduction in risk of death in patients receiving Abraxane as a second line therapy
- FDA approved January 2005 for the treatment of advanced breast cancer after failure of first line chemotherapy



Teng, 2004; Garber, 2004; Tack and Perez, 2004

Dendrimer-based topical microbicide

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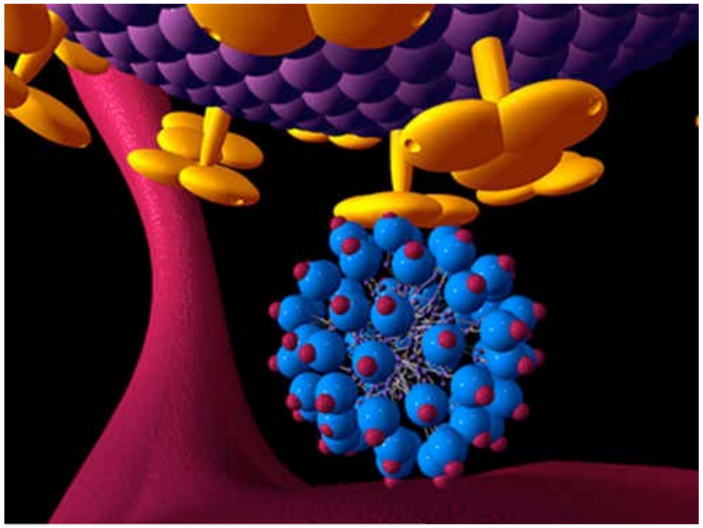
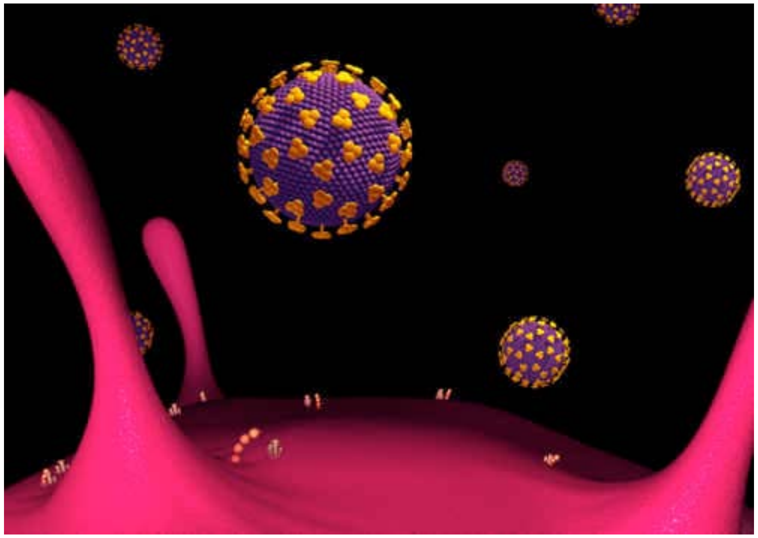
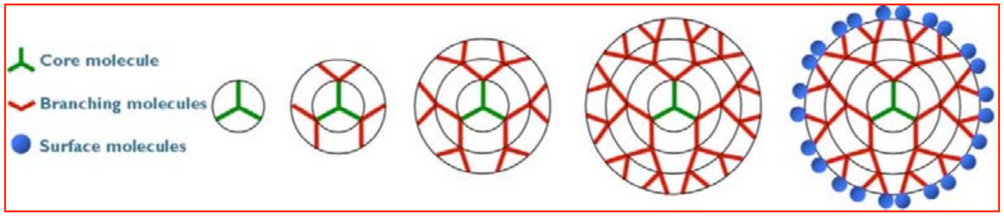
VivaGel is a topical microbicide for prevention of HIV and other STDs. It the first drug product based on dendrimers to enter human trials.



NIAID





Dendrimers

starpharma

- **Fourth-generation polylysine dendrimer called SPL7013**
- **Surface moieties decorate the molecule's surface**
- **Dendrimers bind to the gp120 glycoprotein receptors on the virus's surface**
- **HIV is blocked from attaching to receptors on T cells in the body**

Nanotech Will Enable Targeted Therapies

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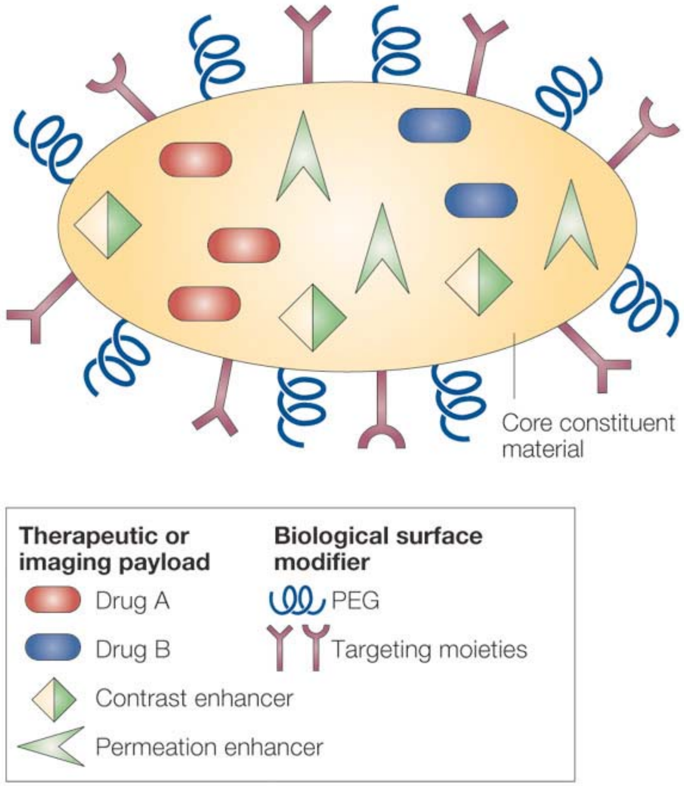
Problem:

- Current treatments - severe side effects
- Current treatments kill healthy cells
- Maintaining effective dose in circulation is difficult
- Multi-drug resistance often occurs

Solution:

- Treatments for controlled and sustained delivery
- Drug-delivery systems that combine targeting agents with efficacy reporters
- Tumor-specific “heat-kill” or “light-kill” treatments

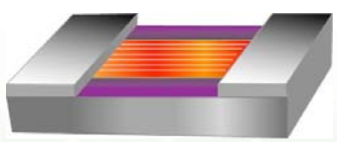


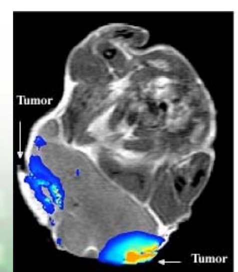
Source: M. Ferrari, “Cancer Nanotechnology: Opportunities and Challenges,” Nature Reviews, March 2005.

Nanotechnology: Cancer Prevention

NCI Alliance for Nanotechnology in Cancer

- Genetic profiling using highly multiplex in-vitro platforms
- Early imaging enabled through the use of ‘smart’ nanoparticles
- Development of in-vivo sensing techniques which will detect (and possibly kill tumor cells) at very early stage
- Reduced discomfort of routine exams – for example endoscopy using in-vivo integrated sensor/imaging/data transfer devices





Nanoproducts Under Development

NCI Alliance for Nanotechnology in Cancer

Product	Type of nanomaterial	Indication	Phase	Company
AmBisome	liposome	fungal infections	approved	Gilead Sciences
Doxil	pegylated liposome	metastatic ovarian cancer	approved	OrthoBiotech
VivaGel	dendrimer	topical microbicide for HIV	Phase I	StarPharma
MRX-952	branching block copolymer self-assembled nanoparticulate formulation of irinotecan metabolite	oncology	preclinical	ImaRx Therapeutics
Definity	lipid-encapsulated octofluoropropane nanospheres	echocardiogram contrast agent	approved	ImaRx/BMS
MRX-815	nanobubbles	vascular thrombosis	Phase I	ImaRx
Abraxane	nanoparticulate albumin	non-small cell lung cancer, breast cancer, others	NDA filed	American Pharmaceutical Partners
Cyclosert-camptothecin	cyclodextrin nanoparticle	metastatic solid tumors	IND filed	Insert Therapeutics
TNT-Anti-Ep-CAM	polymer-coated iron oxide	solid tumors	preclinical	Triton BioSystems
Rapamune	nanocrystalline drug	immunosuppressant for kidney transplantation	approved	Elan/Wyeth
Emend	nanocrystalline drug	nausea	approved	Elan/Merck
Leunesse	solid lipid nanoparticles	cosmetics	on market	Nanotherapeutics
Verigene platform	DNA-functionalized gold nanoparticles	diagnostics	on market	Nanosphere
INGN-401	liposome	metastatic lung cancer	Phase I	Introgen
Combidex	iron oxide nanoparticle	tumor imaging	NDA filed	Advanced Magnetics

M. Ferrari, G. Downing, Biodrugs 19, 203 (2005)

Evolution of Treatment: From Single- to Multi-functional Platforms

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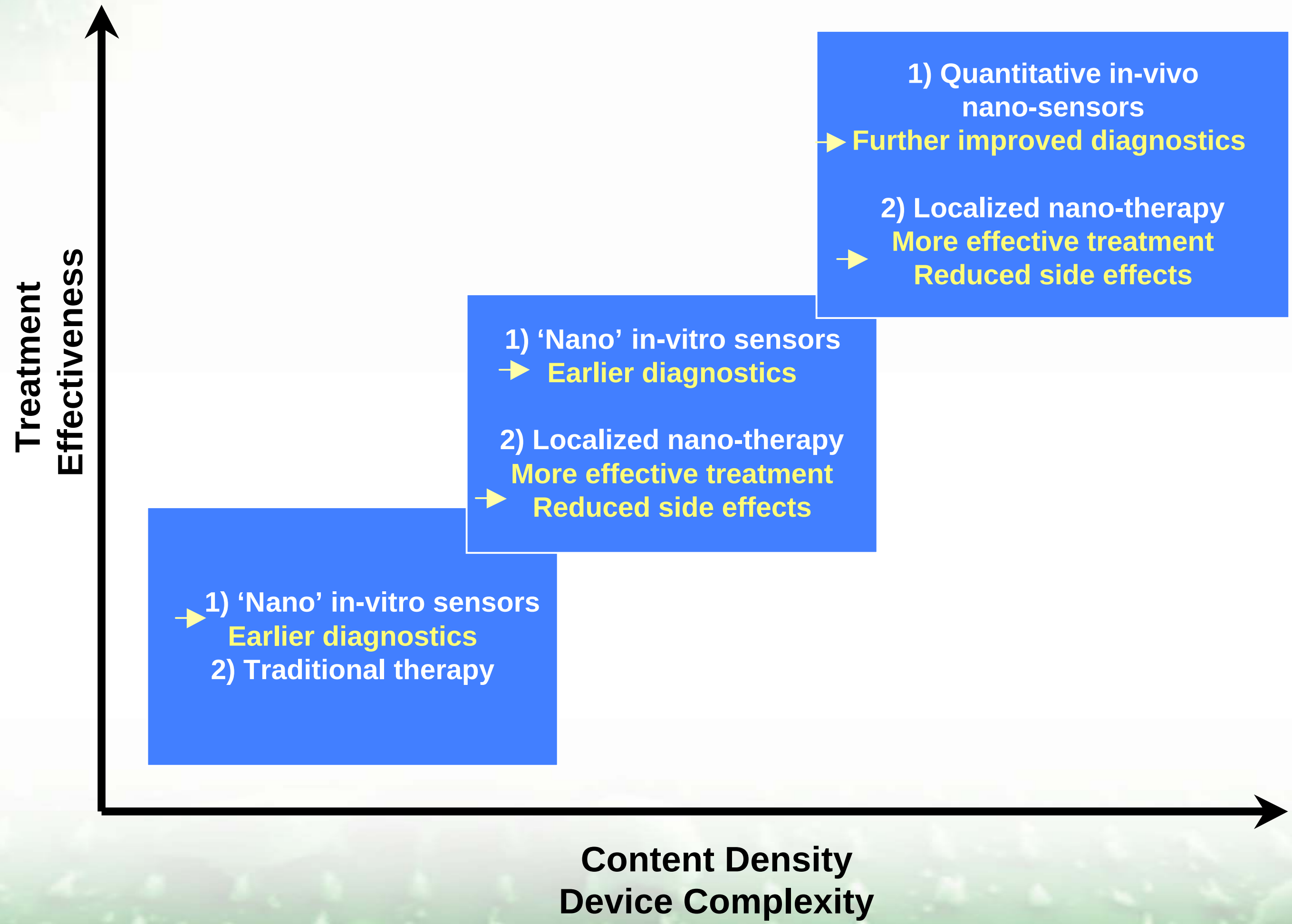


NCI Has Launched the Next Phase of Its Commitment

NCI Alliance for
Nanotechnology
in Cancer

NCI Alliance for Nanotechnology in Cancer

- Launched September 2004
- Designed to “ignite” nano-product development and commercialization
- Encompasses public and private sectors
- Emphasizes cross-disciplinary collaborations
- Defined the need and opportunity for nanotechnology characterization to facilitate medical product development

Alliance Strategies

NCI Alliance for Nanotechnology in Cancer

Major Programs of the Alliance:

1. Centers of Cancer Nanotechnology Excellence
2. Multidisciplinary Research Teams
   - Training
   - Interagency Collaborations
3. Nanotechnology Platforms for Cancer Research
4. Nanotechnology Characterization Laboratory

Centers for Cancer Nanotechnology Excellence

NCI Alliance for Nanotechnology in Cancer

- Carolina Center of Cancer Nanotechnology Excellence, ***University of North Carolina***
- Center of Nanotechnology for Treatment, Understanding, and Monitoring of Cancer, ***University of California, San Diego***
- ***Emory-GA Tech*** Nanotechnology Center for Personalized and Predictive Oncology
- ***MIT-Harvard*** Center of Cancer Nanotechnology Excellence
- Nanomaterials for Cancer Diagnostics and Therapeutics, ***Northwestern University***
- Nanosystems Biology Cancer Center, ***California Institute of Technology***
- The Siteman Center of Cancer Nanotechnology Excellence at ***Washington University***
- ***Stanford*** Center of Cancer Nanotechnology Excellence

Nanobiotechnology Training

NCI Alliance for Nanotechnology in Cancer

- **NCI-NSF Nanobiotechnology Training Collaboration**
- **Bridging cancer biology with NSF IGERT**
- **Current grantees have had training/experience with IGERT**
  - **Integrative Nanoscience and Microsystems**
    Diana Huffaker
    University of New Mexico
  - **NanoPharmaceutical Engineering and Science**
    Fernando Muzzio
    Rutgers University
  - **Nanomedical Science and Technology**
    Srinivas Sridhar
    Northeastern University
  - **Building Leadership for the Nanotechnology Workforce of Tomorrow**
    Marjorie Olmstead
    University of Washington
- **Early pioneers had to blaze their own pathway; this effort lowers the threshhold**
- **Focused interface at grad school level of nanomaterials and cancer biology**
- **Establishes front-end of career development pipeline**

Concepts Underpinning the Nanotechnology Characterization Laboratory

Rationale for the NCL

NCI Alliance for Nanotechnology in Cancer

- Nanotechnology platforms have unique properties yet little known about interaction with biological systems
- Important for medical product development to have identified analytical pathways for characterizing physicochemical and biological responses
- Development of an assay cascade for analysis of representative classes of nanomaterials (initial emphasis on nanoparticles)
- Important insights into efficacy and safety can be attained
- Public data sets of biological and physicochemical data to enable points of reference for product development
- Participation in standards development (ASTM, ANSI)
- Data and information dissemination – cancer Bioinformatics Grid (caBIG)
- Extensive infrastructure, core competencies, and knowledge in product development at NCI-Frederick campus

Key Features of the NCL Development

NCI Alliance for Nanotechnology in Cancer

- Established in 2004 at NCI-Frederick, Ft. Detrick, Maryland
- Development of business plan – prospectus, MTAs, etc.
- Key interactions with nanomaterials developers as source of materials
- Development of nanoplatform prioritization, submissions, and review process
- Scientific Oversight Committee
- Partnership with National Institutes of Standards and Technology and U.S. Food and Drug Administration to facilitate assay development, measurements, and knowledge development
  - Interagency Oncology Task Force Subcommittee activity
  - Component of FDA Critical Path Initiative
  - Training opportunities
- Participant in National Nanotechnology Initiative activities in nanotechnology assessment
- Substantial communications program in support of nanotechnology safety assessment (e.g., patient advocates, community outreach, and Woodrow Wilson Project)

Ongoing NCL Program Development

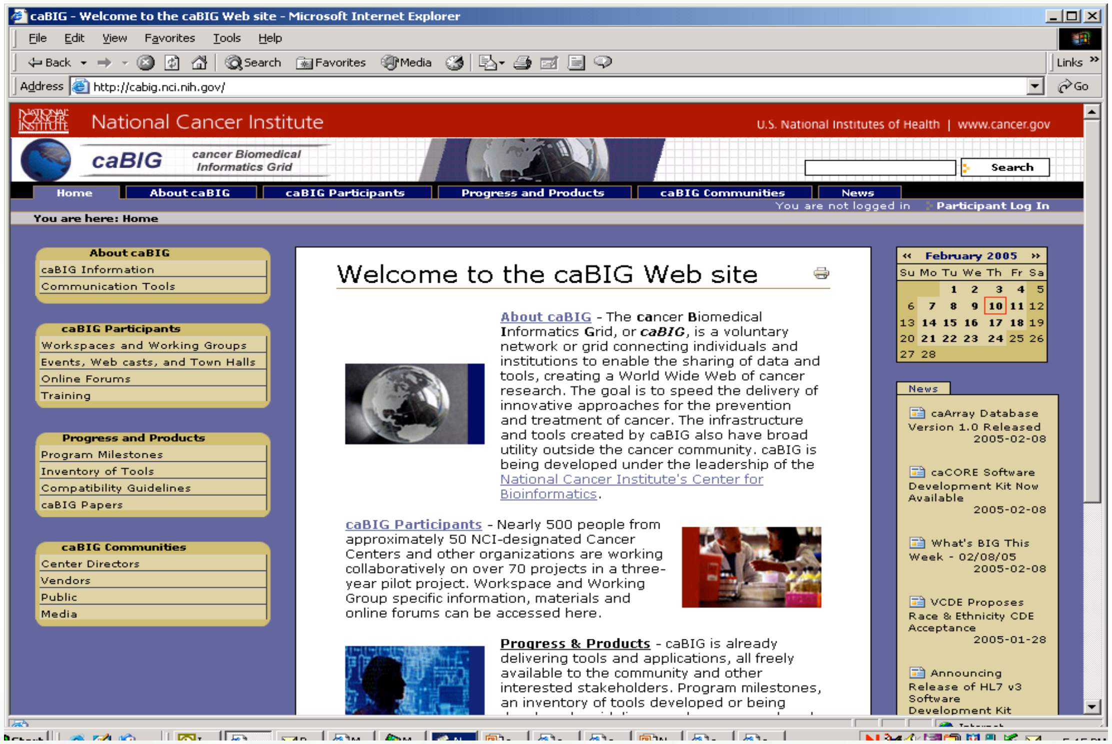
- Applying imaging technologies in assay cascade
  - Biodistribution studies
  - Methods development
- Additional partnership opportunities
  - NIEHS
  - Other federal laboratories
  - National Library of Medicine
- Data integration and information dissemination
  - caBIG interactions linking CCNEs and NCL
  - Laboratory Information System
  - Publicly available data base – FDA interactions

cancer Biomedical Informatics Grid (caBIG)
http://cabig.nci.nih.gov

NCI Alliance for Nanotechnology in Cancer

"A virtual web of interconnected data, individuals, and organizations that re-defines how research is conducted, care is provided, and patients/participants interact with the biomedical research enterprise"

- Common, widely distributed infrastructure permits cancer research community to focus on innovation
- Shared vocabulary, data elements, data models facilitate information exchange
- Collection of interoperable applications developed to common standard
- Raw published cancer research data is available for mining and integration



Core LIMS Goals- caLAB

NCI Alliance for Nanotechnology in Cancer

- To develop a core caBIG compliant LIMS that follows the caBIG principles (caLAB –cancer Laboratory Analysis Bench)
  - Open Source
  - Open Access
  - Interoperability (Syntactic and Semantic) via standard Common Data Elements (CDEs) and Terminology
- To develop a core LIMS that can be utilized by a variety of laboratories operating diverse experiment modalities (NCL, NIST)
- To develop a core generic LIMS that can be customized and extended to support laboratory specific requirements (CCNEs)
- To create an affordable (free) “near” commercial grade LIMS that allows laboratories to focus on scientific research and scientific investments

Goals for NCL caLAB Development

NCI Alliance for Nanotechnology in Cancer

- To capture and manage assays and assay results throughout the NCL laboratory workflow
- To capture the nanoparticle characterizations and leverage these characterizations in the development of industry standards (CDEs, ontologies, assays) supporting nanotechnology
  - Allows for data sharing between diverse scientific communities
  - Facilitates new scientific discoveries
- To propagate approved research data to authorized centers/collaborators through caBIG
- Facilitates information transfer to establish a publically accessible data file of medical products in development

The Interface of Toxicology Studies in Medical Product Development and Environmental Health and Safety Assessment

Lessons Learned

NCI Alliance for Nanotechnology in Cancer

- Important to identify commonalities and distinguish differences in needs and approaches for toxicology studies in medical product development and environmental health sciences (i.e., route of administration and exposure)
- We have learned the importance of public understanding and value assignment of new technologies (i.e., recombinant DNA technology)
- Transparency of the intended applications of R&D is important
- Understanding of individual and society level risk-benefit profiles for dose-exposure (e.g., chemotherapeutic vs. chemopreventive agents)
- Recognition that the NTP program itself has some characteristics of all of these

Understanding Human Risk

NCI Alliance for Nanotechnology in Cancer

- **Hazard identification**
  - **In vitro toxicity**
  - **Acute in vivo toxicity**
  - **Subchronic/chronic toxicity**
  - **Route of exposure**
- **Dose response**
  - **External dose**
  - **Internal dose**
  - **Biologically effective dose**
- **Exposure assessment**
  - **Human exposure**

Nanomaterials production

↓

Chronic exposure of the worker

Nanomaterials use for biomedical applications

↓

Dose and patient response

N. Walker, NIEHS

Where are We Now?

NCI Alliance for **Nanotechnology** in Cancer

- Recognition that strategies are needed to broaden understanding the interactions of nano-engineered materials with life systesm
- Public databases and integrated knowledge about physicochemical and biological interactions are crucial to acceptance of technologies – medical applications are highly valued
- Further exploration is needed on how assays and data from medical product development can facilitate EHS approaches
- Toxicological studies provide insights into biology.[1]

[1] Nei A. et al., Toxic potential of materials at the nanolevel. Science 2006:311;622.

Challenges and Opportunities

Challenges

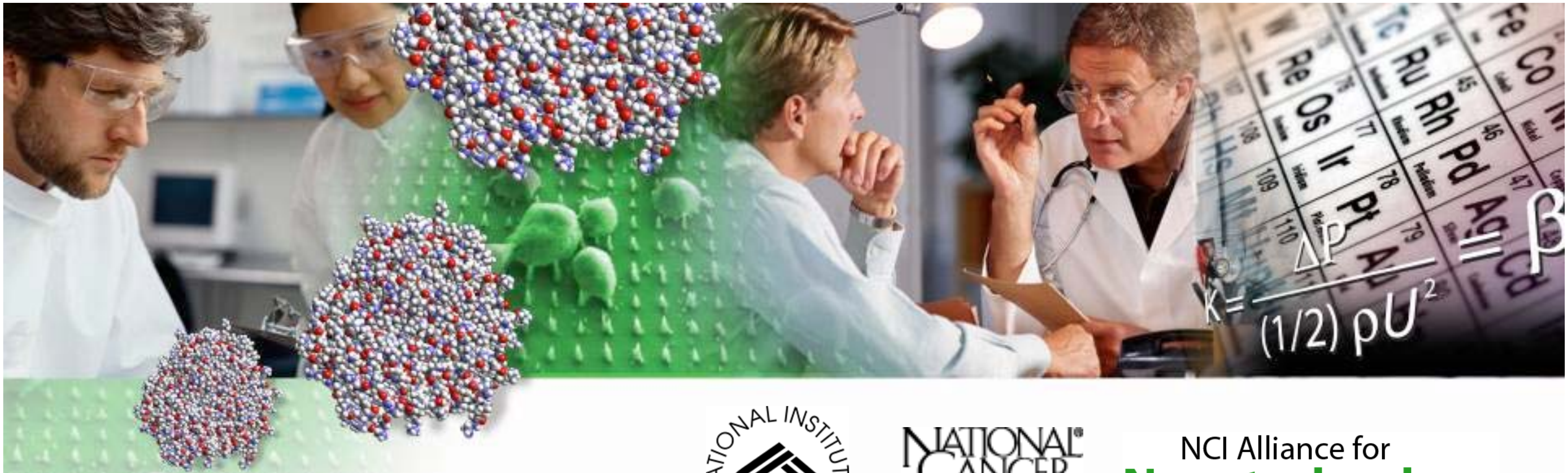
NCI Alliance for Nanotechnology in Cancer

- Vast array of nanomaterials and little known about biophysical interface – priorities are needed
- Uniqueness of nanoscale compositional or molecular structure changes on functional affects
- Lack unified nomenclature and standards
- Maintaining scientific rigor and high level of scrutiny of model systems, data, and inferences

Opportunities

NCI Alliance for Nanotechnology in Cancer

- Extension of NCL resources: assays, data sets, informatics platforms, training, facilities
- Exploration of potential interfaces with NTP approaches and mechanisms
- New models for partnership with private sector and other Federal agencies



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